Attorney Docket # 4804-4

14/ Priority Papers

Patent

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of

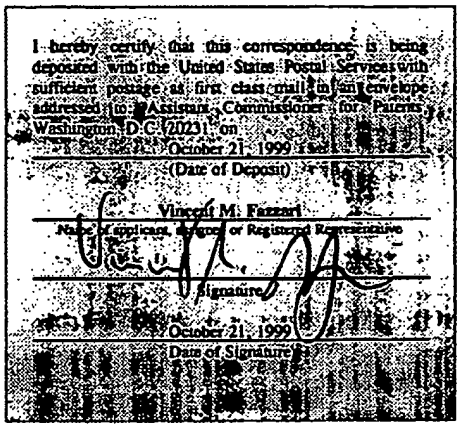
Stephan Lukas et al.

Serial No.: 09/177,427

Filed: October 22, 1998

For: Taste Masked Pharmaceutical Compositions

Examiner: Berman, A.
Group Art: 1615

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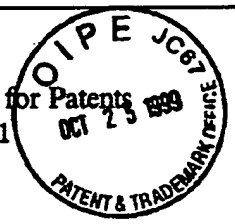


**LETTER TRANSMITTING PRIORITY DOCUMENTS**

In order to complete the claim to priority in the above-identified application under 35 U.S.C. §119, enclosed herewith is a certified copy of each foreign application on which the claim of priority is based:

Australian Application No. PN9407 filed April 23, 1996,

Australian Patent Application No. PO6371 filed on April 23, 1997,

International Phase PCT Application No. PCT/AU97/00248 filed April 23, 1997.

and

International Phase PCT Application No. PCT/AU98/00296 filed April 23, 1998.

Respectfully submitted,
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In 09/177,427

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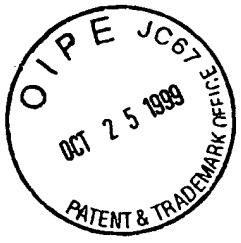
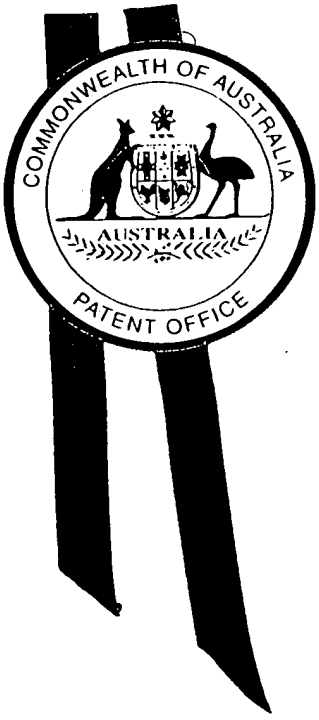



**Patent Office**
**Canberra**

I, KIM MARSHALL, MANAGER EXAMINATION SUPPORT AND SALES, hereby certify that the annexed is a true copy of the Provisional specification in connection with Application No. PN 9407 for a patent by F.H. FAULDING & CO. LIMITED filed on 23 April 1996.

**CERTIFIED COPY OF PRIORITY DOCUMENT**




WITNESS my hand this Fourth
day of June 1999

KIM MARSHALL
MANAGER EXAMINATION SUPPORT AND SALES

**AUSTRALIA**
**Patents Act 1990**

# PROVISIONAL SPECIFICATION

Applicant: F.H. FAULDING & CO. LIMITED

Invention Title: TASTE MASKED PHARMACEUTICAL COMPOSITIONS

AUSTRALIAN
PROVISIONAL NO. DATE OF FILING
PN9407 23APR.96
PATENT OFFICE

The invention is described in the following statement:

## Taste Masked Pharmaceutical Compositions

The present invention relates to a pharmaceutical composition, in particular to a taste masked pharmaceutical composition having improved coating characteristics, preferably having less than 23% by weight coating material and a method of preparing such a composition preferably incorporating a spray drying technique.

Many pharmaceutical drugs have unpleasant tastes and therefore the oral administration of the pharmaceutical drug is often an unpleasant experience, particularly for those who find it difficult to swallow whole dosage forms. The pharmaceutical drug remains in the mouth for a time sufficient to impart its unpleasant taste sometimes resulting in the patient expelling the dosage form.

Artificial flavourings and sweeteners have often been used to mask the taste by generally overwhelming the taste of the pharmaceutical however, these are often unsuccessful and the bitter taste remains in the taste or remains as a lingering after taste if small particles of drug linger in the mouth.

Other methods of masking the taste include coating the drug with a polymeric material such as ethyl cellulose or a lipid based formulation such as paraffins, waxes, beeswax, higher fatty acids, higher fatty acid esters, glycerin fatty acid esters, and/or poly propylene glycols so as to create a barrier and delay the dissolution of the drug. However, these lipid based formulations are generally not effective at taste masking on their own and often require a polymer such as ethyl cellulose to complete the taste masking of the drug.

In US 4,767,789, ethyl cellulose has been used to coat acetaminophen to mask the bitter taste. However, the limit of acetaminophen is 24% by weight and it is explicitly stated that taste masking of acetaminophen is not achieved if the ethyl

cellulose falls below this limit. Spray drying processes used to coat acetaminophen fail to provide taste masking at low ethyl cellulose concentrations as the coat is generally porous and irregular with roughened surfaces and this leads to ineffective taste masking due to rapid release of the pharmaceutical from the dosage form.

It would be desirable to provide a pharmaceutical composition form having a low ethyl cellulose concentration which improves taste masking and bioavailability of the pharmaceutical. The present applicants have surprisingly found that pharmaceutical's can be taste masked with a coating material, preferably ethyl cellulose as low as 23% and less. Preferably the pharmaceutical is coated by using a spray drying technique.

Accordingly, it is the object of the present invention to overcome or at least alleviate one or more of the difficulties related to the prior art by providing a taste masked composition which uses less coating material. This improvement may enhance bioavailability of the drug and reduce the cost in providing a taste masked formulation.

Accordingly, in a first aspect of the invention there is provided a taste masked pharmaceutical composition including:

a core element including a pharmaceutically active ingredient; and

a coating material of less than 23% by weight of the total weight of the composition including a polymer wherein said coating material provides a substantially continuous coating on the core element.

Preferably the pharmaceutical composition includes

approximately 90% to 77%, preferably 90 to 80% by weight, based on the total weight of the composition of a core element including at least one pharmaceutically active ingredient; and

approximately 10 to 23%, preferably 10 to 20 by weight of a substantially continuous coating on the core element formed from a coating material including a polymer.

The core element in the coated pharmaceutical composition according to the present invention preferably may include up to 100% by weight of the pharmaceutically active ingredient.

The core element may further include carriers or excipients, fillers, flavouring agents, stabilizing agents and colourants. Suitable fillers may be selected from insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose and mixtures thereof. Soluble fillers may be selected from mannitol, sucrose, lactose, dextrose, sodium chloride, sorbitol and mixtures thereof.

The filler may be present in amounts of up to approximately 75% by weight based on the total weight of the composition.

The core element may be of any suitable particle size. Particle sizes of approximately 0.1 to 250μm have been found to be suitable. Particle sizes of approximately 35 to 125μm have been found to be particularly suitable.

The pharmaceutically active ingredient may be any drug, preferably a bad tasting drug. The term "bad tasting drug" includes those drugs which are perceived to have a bitter, acid, or salty taste but are not restricted to these tastes. It may also include drugs which irritate the oral mucosa. The pharmaceutically active ingredient may be selected from any one of the following:

Antacids, anti-inflammatory substances, coronary dilators, peripheral vasodilators, anti-infectives, psychotropics, anti-manics, stimulants, anti-histamines,

laxatives, decongestants, vitamins, gastro-intestinal sedatives, anti-diarrhoeal preparations, anti-anginal drugs, vasodilators, anti-arrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anti-coagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseates, anti-convulsants, neuromuscular drugs, hyper-and hypoglycaemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, bronchodilators, expectorants, cough suppressants, mucolytics, anti-ulcer and anti-uricemic drugs;

Gastro-intestinal sedatives such as metoclopramide and propantheline bromide, Antacids such as aluminium trisilicate, aluminium hydroxide and cimetidine;

Anti-inflammatory drugs such as phenylbutazone, indomethicin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone, and prednisone;

Coronary vasodilator drugs such as glyceryl trinitrate, isosorbide dinitrate and pentaerythritol tetranitrate, peripheral;

Cerebral vasodilators such as soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cylandelate, papaverine and nicotine acid;

Anti-infective substances such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate and hexamine hippurate;

Neuroleptic drugs such as flurazepam, diasepam, temazepam, amitryptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylimipramine;

Central nervous stimulants such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride;

Antihistamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine;

Anti-diarrheal drugs such as bisacodyl and magnesium hydroxide, the laxative drug, dioctyl sodium sulfosuccinate;

Nutritional supplements such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine;

Anti-spasmodic drugs such as dicyclomine and diphenoxylate, drugs affecting the rhythm of the heart such as verapamil, nifedipine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate;

Drugs used in the treatment of hypertension such as propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril and hydralazine;

Drugs used in the treatment of migraine such as ergotamine;

Drugs affecting coagulability of blood such as epsilon aminocaproic acid and protamine sulfate;

Analgesic drugs such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodeinone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid;

Anti-epileptic drugs such as phenytoin sodium and sodium valproate;

Neuromuscular drugs such as dantrolene sodium;

Substances used in the treatment of diabetes such as tolbutamide, disbenase glucagon and insulin;

Drugs used in the treatment of thyroid gland disfunction such as triiodothyronine, thyroxine and propylthiouracil;

Diuretic drugs such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and trimterone, the uterine relaxant drug ritodrine;

Appetite supressants such as fenfluramine hydrochloride, phentermine and diethylproprion hydrochloride;

Anti-asthmatic and bronchodilator drugs such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate;

Expectorant drugs such as guaiphenesin, cough suppressants such as dextromethorphan and noscapine;

Mucolytic drugs such as carbocisteine;

Anti-septics such as cetylpyridinium chloride, tyrothricin and chlorhexidine;

Decongestant drugs such as phenylpropanolamine and pseudoephedrine, hypnotic drugs such as dichloralphenazone and nitrazepam;

Anti-nauseant drugs such as promethazine theoclate;

Haemopoietic drugs such as ferrous sulphate, folic acid and calcium gluconate; and

Uricosuric drugs such as sulphinpyrazone, allopurinol and probenecid.

Particularly preferred drugs are:

Ambroxol, ibuprofen, paracetamol, 5-amino-salicylic acid, dextromethorphan, propranolol, theophylline, diltiazem, methyldopa, pseudoephedrine, cimetidine, cephalexin, cephaclor, cephradine, naproxen, piroxicam, diazepam, diclofenac,

indomethicin, amoxycillin, pivampicillin, bacampicillin, dicloxacillin, erythromycin, erythromycin stearate, lincomycin, co-dergocrine mesylate, doxycycline, dipyridamole, frusemide, triamterene, sulindac, nifedipine, atenolol, lorazepam, glibencalamide, salbutamol, trimethoprim/sulphamethoxazole, spironolactone, carbinoxamine maleate, guaiphenesin, potassium chloride and metoprolol tartrate.

Especially preferred drug includes paracetamol, cimetidine, dextromethorphan, ambroxol, risperidone and ibuprofen. Most preferably the drug is paracetamol.

The coating material may include a polymer including at least one of the following methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), poly (hexyl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), poly (ethylene), poly (ethylene) low density, poly (ethylene)high density, (poly propylene), poly (ethylene glycol), poly (ethylene oxide), poly (ethylene terephthalate), poly(vinyl alcohol), poly(vinyl isobutyl ether), poly(viny acetate), poly (vinyl chloride) and polyvinyl pyrrolidone.

Preferably the polymer is a water insoluble polymer.

Preferably the polymeric coating material includes ethyl cellulose.

The water insoluble polymer preferably may be selected from ethyl cellulose or dispersions of ethyl cellulose such as those sold under the trade designation Aquacoat

or Surelease, acrylic and/or methacrylic ester polymers, cellulose acetates, butyrates or propionates or copolymers of acrylates or methacrylates having a low quaternary ammonium content and the like.

Preferably the polymeric coating material includes ethyl cellulose.

The coating material is less than 23% of the total weight of the composition and still effectively provides taste masking, however it is preferable that the coating material constitute less than 20% of the total composition and still provide taste masking.

The coating material according to this aspect of the present invention may further include at least one plasticiser.

The plasticiser may be selected from diethyl phthalate, triethyl citrate, triethyl acetyl citrate, triacetin, tributyl citrate, polyethylene glycol, propylene glycol, glycerol, dibutylsebacate, castor oil and the like.

The plasticiser may be present in amounts from 0 to approximately 50% by weight based on the total weight of the coating.

The coating material according to the present invention may take any suitable form which provides a continuous coating and still provides taste masking.

The substantially continuous coat is substantially hole-free. The substantially continuous nature of the coating may be achieved by spray drying from a suspension or dispersion of the pharmaceutically active ingredient in a solution of the coating composition including a polymer in a solvent in a drying gas having a low dew point. The dew point may preferably be less than 0°C, more preferably less than approximately -15°C.

By "substantially continuous coating" we mean a coating which retains a smooth and continuous appearance when magnified 1000 times under a scanning electron

microscope and wherein no holes or breakage of the coating is evident so as to reduce taste masking.

Typical coatings may be in the range of approximately 0.005 to 25μm to, preferably approximately 0.05μm to 5μm. It will be understood, accordingly, that the rate of absorption may be modified by modifying the thickness and/or the composition of the coating material.

The solvent which may be used in the preparation of the coating of the composition may be an organic solvent. The solvent may be such that it constitutes a good solvent for the coating material but it is substantially a non-solvent or poor solvent for the pharmaceutically active ingredient. Whilst the active ingredient may partially dissolve in the solvent, in this aspect of the invention, the active ingredient will precipitate out of the solvent during the spray drying process much more rapidly than the coating material.

The solvent may be selected from alcohols such as methanol, ethanol, halogenated hydrocarbons such as dichloromethane (methylene chloride), hydrocarbons such as cyclohexane, and mixtures thereof. Dichloromethane (methylene chloride) has been found to be particularly suitable.

The concentration of polymer in the solvent will normally be less than 75% by weight. Normally the concentration will be in the range of 10-30% by weight.

Where the polymer is ethyl cellulose, the solvent is preferably methylene chloride. The concentration of ethyl cellulose is preferably in the range of 5-10% most preferably 7% by weight based on the total concentration of the coating material.

The pharmaceutically active ingredient, provided in a form suitable for coating may be suspended in the coating material/organic solvent solution, preferably in an

ethyl cellulose/methylene chloride solution at a concentration in the range of 10-30% by weight, preferably in the range of 14-20% by weight.

In a preferred aspect of the invention there is provided a taste masked pharmaceutical composition including:

a core element including a pharmaceutically active ingredient; and

a coating material of less than 23% by weight of the total weight of the composition including a polymer wherein said coating material provides a substantially continuous coating on the core element;

said composition exhibiting a reduced dissolution profile.

The dissolution profile of the microcapsule composition may be reduced by approximately 25%, preferably approximately 40%, more preferably approximately 50%, relative to a standard microencapsulated form, when measured at a pH approximately that of the mouth, for example a pH of approximately 6.8 in the period of 0 to approximately 45 minutes, preferably 0 to approximately 20 minutes.

By "dissolution profile" as used herein, we mean a plot of amount of active ingredient released as a function of time. The dissolution profile may be measured utilising the Drug Release Test (724) which incorporates standard test USPXXII 1990. (Test (711) Supplement VI, 1992). The dissolution tests are conducted in a modified flow through cell apparatus. A profile is characterised by the test conditions selected. Thus the dissolution profile may be generated at a preselected temperature, flow rate and pH of the dissolution media.

Accordingly, the present invention further provides a taste masked pharmaceutical composition including:

a core element including at least one pharmaceutically active ingredient; and

a coating material of less than 23 % by weight of the total weight of the composition including a polymer, and

wherein the core element is selected for a size in the range of 0.1μm to 250μm and shape which facilitates coating and provides a continuous coating on the core element.

Applicants have found that the successful taste masking greatly depends on the completeness of the coating. This may be influenced by parameters such as the size and shape of the core element to be coated. Where the size and shape is favourable for coating very low levels of coating material can be used to coat the core element such that taste masking and a continuous coating is achieved.

The particle size distribution of the core element dictates the surface area to be coated. If the core element is too small, very large surface areas need coating.

The size of the core element is generally selected so that there will be no substantial breakage of the coat if the pharmaceutical composition is masticated so as to cause immediate release of the drug leaving a very distinctive unpleasant taste. The particles are preferably small enough to pass into curves and depressions in the mouth and between the teeth and avoid substantial breakage. Small particles may also pass through the stomach quickly and made available for absorption in the intestine. Therefore, the pharmaceutical can reach the blood stream much faster.

Preferably the size of the core element including the pharmaceutically active ingredient is in the range of 0.1μm to 250μm, most preferably the range of 35μm to 125μm.

Shape can also influence the coverage and stability of the coat. Sharp angles on a crystal can cause weaknesses in the coat. These sharp corners may lead to

stress points on the coat and cause weaknesses in the structure possibly leading to premature release of the pharmaceutical from the pharmaceutical composition.

The coat is thinner at the vertices also leading to more rapid release.

The composition according to the present invention is applicable to pharmaceutically active ingredients having a crystalline morphology and particularly a low aspect ratio. As the crystal geometry may result in a relatively thin coat at the crystal needle tips the release rates may be more rapid than is preferred with such actives. Similarly, where the pharmaceutically active ingredient exhibits high water or organic solvent solubility, the release rates may be more rapid than is required in a particular application. Furthermore, areas of thin coating are susceptible to breaking and cracking and hence ineffective for taste masking.

Applicants have found that a spherical shape of the particle is most advantageous for both stability of the coat and high payload of active pharmaceutical.

It is also preferable for all particles to be of the same size and shape. Inconsistencies in size and shape can lead to inconsistent coating. Where the drug particles are of different size and shape, polymeric coating materials such as ethyl cellulose will deposit differently on each particle. It is therefore preferable to have all particles the same size and shape so that the coating process is better controlled and maintained.

Accordingly, in a preferred form, the composition may include a core element comprising approximately 90% to 77% by weight based on the total weight of the composition, said core element including:

approximately 52 to 85% by weight of a pharmaceutically active ingredient; and

approximately 5% to 25% by weight of a supplementary component selected from waxes, water insoluble polymers, enteric polymers, and partially water soluble polymers and other suitable pharmaceutical excipients.

The supplementary component may be provided as an intimate mixture with the active ingredient or as a precoat thereon. Where an intimate mixture is formed, polymers such as hydroxypropyl methyl cellulose may be used.

Where a precoat is formed, a wax coat is preferred. A paraffin wax or a canauba wax may be used. In a preferred form the pharmaceutically active ingredient is a compound of high water or solvent solubility and the supplementary component forms a precoat on the active ingredient.

By "high solubility", we mean solubility of greater than 1 in 30.

The present invention also provides a method of preparing a taste masked pharmaceutical composition including :

a core element including a pharmaceutically active ingredient; and

a coating material of less than 23% by weight of the total weight of the composition including a polymer wherein said coating material provides a substantially continuous coating on the core element;

which process includes:

providing a sufficient amount of:

at least one pharmaceutically active ingredient selected for a size in the range of 0.1m to 250μm and shape suitable for coating to provide a continuous coating;

a solution of a coating material including a polymer and an organic solvent being selective for the polymer;

suspending or dispersing the pharmaceutically active ingredient in the solution of coating material;

spray drying the suspension or dispersion of pharmaceutically active ingredient in a dry gas having a low dew point; and

collecting the pharmaceutically active ingredient having a coating of polymeric coating material of less than 23% by weight based on the weight of the total weight of the composition.

In a further preferred aspect of the invention, the method includes a preliminary step of pre-coating a pharmaceutically active ingredient in a shaping medium before coating with a water insoluble polymer. The size and shape of the particle is important for obtaining a coating with less than 23% w/w of the total composition and still maintain taste masking. Where the particles are of an incorrect size or shape, the particle of drug may be precoated with shaping medium which may include a binder, filler, excipient or lubricant as used in the tabletting technology to obtain a size and shape suitable for coating so as to obtain an even coat which is continuous and thereby provide taste masking.

A "shaping medium" as used herein is a compound or composition which can be shaped, manipulated or moulded in or around a body such as a pharmaceutically active ingredient such that upon shaping, manipulating and moulding, the body and shaping medium together take on a new form. The shaping, manipulating and moulding may be used to smooth sharp angles on crystals, increase the size of the body or prepare the body so that the body is more favourably shaped for coating with polymer.

The use of wax is a suitable shaping medium and can serve to obtain a size and shape of the drug so that a favourable size and shape is obtained. For some drugs,

such as pseudoephedrine, the drug may be irregular in shape, or too small. The wax serves to obtain regularity of shape, increase the size of the drug particle, or shape with the drug particle to provide a more favourable shape of particle for coating if necessary.

The wax may also serve to delay dissolution of the drug once it enters the body or partly act to enhance taste masking. The wax may act as a hydrophobic barrier to liquids such as saliva and gastric juices.

The drug may also be incorporated in a matrix of binder and filler which can also be coated with wax to obtain a consistent size and shape suitable for coating. Suitable binders and fillers are familiar to those skilled in the art.

Wax coating of the particles can be performed by a process of preparing a slurry of molten wax which is heated to melt the wax but not degrade the pharmaceutically active ingredient. The molten slurry of wax and pharmaceutical may then be atomized preferably using a 2 fluid nozzle into a spray dryer to form core particles which may then be further coated with a coating material such as a polymer to provide taste masking.

The pharmaceutical drug may be any drug as listed previously, without limitation. Preferably the drug is one selected from paracetamol, cimetidine, ambroxol, pseudoephedrine, dextromethrophan, risperidone, or ibuprofen. Most preferably, the pharmaceutical drug is paracetamol.

For paracetamol, it is preferable that the particles be in the range of 50-150μm and are spherical in shape.

Spray drying of the pharmaceutically active ingredient and polymer in the solvent involves spraying a stream of air into an atomised suspension so that solvent is caused to evaporate leaving the pharmaceutical drug coated with the polymer coating material.

Preferably, for a solvent such as methylene chloride, the solvent concentration in the drying chamber is maintained above 40,000 parts, more preferably in the range of approximately 40,000 to 100,000 parts per million of organic solvent.

The spray-drying process for such solvents may be conducted at a process temperature of from approximately 5°C to 35°C.

The utilisation of a drying gas exhibiting a low dew point aids the production of a substantially continuous coating. It has also been found that the presence of a solvent during the drying step slows the evaporation rate of the solvent such that a substantially continuous coat exhibiting reduced permeability is produced. The concentration of non-solvent (e.g. water) present should be kept very low and that, in combination with the controlled drying conditions, results in microcapsules with continuous coats. These two factors may be interrelated. Thus the higher the drying gas dew point, the higher the solvent vapour pressure required in the system to give a substantially continuous coat.

The drying process may be of any suitable type.

Spray drying of the pharmaceutical compositions may be undertaken utilising either rotary, pneumatic or pressure atomisers located in either a co-current, counter-current or mixed-flow spray dryer or variations thereof. However the chamber should be substantially free of precipitant or non-solvent during processing.

The drying gas may be of any suitable type. Nitrogen or air may be used. The air should be substantially dry and pure. It has been found that the dryness of the drying gas and/or atomising gas may affect the quality of the microcapsule coat formed. The drying gas dew point may more preferably be maintained in the range of from approximately -15°C to -30°C. The atomising gas may be the same as, or similar to, the drying gas.

The drying gas may be heated or cooled to control the rate of drying. A temperature below the boiling point of the solvent may be used. Inlet temperatures will typically be in the range of from approximately 40°C to 120°C and outlet temperatures approximately 5°C to 35°C. Control of temperature may also affect the quality of microcapsule coat formed.

The present invention permits the optimisation of the coat formation to meet the needs of the material or application. Adjusting the coating composition allows modification of the release profile for the material. Controlling the process parameters including temperature, solvent concentration, spray dryer capacity, atomising air pressure, droplet size, viscosity, total air pressure in the system and solvent system, allows the formation of range of coats, ranging from dense, continuous, non-porous coats through to more porous microcapsule/polymer matrices.

The spray drying process may utilise a method employing a nozzle to atomise the drugs in polymeric coating material/organic solvent solution. Preferably pneumatic atomisation is used. The nozzle produces individual droplets with a single unit of drug suspended in a polymeric coating material/organic solvent solution. Removal of the organic solvent results in a drug dosage unit coated with the polymeric coating material.

Preferably the nozzle is a 2 fluid nozzle. The ratio of solvent/drug to air is important in a 2 fluid nozzle and this may be varied by optimizing the relative positions of the outlet and inner passages. The operating conditions include variations on air inlet temperatures, air outlet temperatures, air pressures, feed rates of solvent and drug suspensions, atomisation, air quality and outlet diameters of inlet and outlet passages of the atomizer. Preferably, the air inlet temperature is approx 70-150°C, the air outlet temperature is in the range of 20-50°C, the air flow rate is in the range of 40-1300kg/hr,

the feed rates of solvent and drug is in the range of 3-75 kg/hr, atomisation air quantity is in the range of 6-60 kg/hr and the outlet diameter of the inlet and outlet passages are approximately 2-6 mm and 4-12 mm in diameter respectively.

More preferably, the air inlet temperature is approx 100°C, the air outlet temperature is in the range of 25-35°C, the air flow rate is in the range of 40-80kg/hr, the feed rates of solvent and drug is in the range of 8-9 kg/hr, atomisation air quantity is in the range of 7-9 kg/hr and the outlet diameter of the inlet and outlet passages are approximately 2-3 mm and 4-6 mm in diameter respectively.

The product may be collected by any means available to the skilled addressee. Preferably the collection method is by sock filters or cyclone collection.

The final product will have a polymeric coating of less than 23% by weight and still maintain taste masking. Preferably the final product is paracetamol having 79-84% by weight paracetamol and 16-21% by weight ethyl cellulose.

Most preferably, the paracetamol is a taste masked composition of 80% by weight paracetamol and 20% by weight ethyl cellulose. The average size of the paracetamol final product is approximately 125μm.

Accordingly, the present invention further provides in a preferred aspect a post-treatment step to remove residual solvent. The post treatment may include a post drying step including drying the final product on a tray and drying the product at a bed temperature sufficient to remove excess solvent but not degrade the pharmaceutical drug. Preferably the temperature is in the range of 35°C to 45°C, most preferably at 40°C.

The pharmaceutical composition may be in the form of microcapsules which have a particle size of approximately 300μm or less, preferably approximately 75 to

150μm. The small particle size ensures that the particles have a substantially non-gritty feel in the mouth. The small particle size may also minimise break-up of the microcapsules in the mouth, eg by the teeth.

The taste masked pharmaceutical composition may be further provided in any suitable unit dosage form. The pharmaceutical composition may be provided in a form selected from sprinkles, sachets, chewing gums, tablets; including chewable tablets, gums, lozenges, liquids, suspensions, filled capsules; including filled gelatine capsules. the pharmaceutical composition may be provided in the form of dispersible or effervescent tablets.

The present invention will now be more fully described with reference to the accompanying examples. It should be understood, however that the following description is illustrative only and should not be taken in any way as a restriction on the generality of the invention as specified above.

## Example 1

### Cimetidine Formulae and Process

**Powder formulation**:

| **Component** | **% Composition** |
|---|---|
| cimetidine | 67% |
| ethylcellulose | 33% |
| methylene chloride | N/A |

**Powder process:**

Ethylcellulose (the coating polymer) is first dissolved in methylene chloride (7.7% by weight). The required amount of cimetidine is then added and stirred until an even suspension is formed. The cimetidine does not dissolve to any significant extent.

This suspension is then spray dried using pneumatic atomisation. General process conditions are as follows:

| | |
|---|---|
| Inlet air temperature: | 100°C |
| Outlet air temperature: | 25-35°C |
| Slurry spray rate: | 8-9 kg/hour |
| Process air quantity: | 40-80 kg/hour |
| Atomisation air quantity: | 7-9 kg/hour |
| Fluid insert diameter: | 2.6mm |
| Air cap diameter: | 5.0mm |

The slurry was delivered using a Watson Marlow peristaltic pump. The spray dryer used was a Niro Atomiser Mobile Minor modified to include a 1m extension to the drying chamber and with a speed controller on the turbine to control the process gas quantity.

Powdered product was collected using Goretex sock filters. Excess residual solvent was removed from the powder by a post drying step. This involved a simple tray drying of the powder at a bed temperature of approximately 40 °C.

## Example 2

## Taste-Masked Pseudoephedrine

### 2.1 Wax Coating

Pseudoephedrine HCl: 55g

Carnauba wax: 45g

Heated to 105°C to melt the carnauba wax but not degrade the pseudoephedrine. The molten slurry is then atomised using a 2 fluid nozzle into a standard spray dryer to form spherical, hard core particles.

**2.2 Polymer Coating of Core Particle**

Pseudoephedrine cores from above: 100g

Ethylcellulose: 100g

Methylene chloride: 1800g

The polymer is firstly dissolved in the solvent then the cores added while stirring by means of a mechanical overhead blade stirrer.

This slurry of cores in polymer solution is again atomised using a 2 fluid nozzle atomiser into a spray dryer using conditions similar to Example 1.

Finally it is to be understood that various other modifications and/or alterations may be made without departing from the spirit of the present invention as outlined herein.